REMARKS

Claims 1, 3, 4, 6, and 10-12 are pending.

The amendment to claim 1 is supported by the specification at page 6, the 11th to 13rd lines from the bottom. The amendment to claim 12 would not narrow the scope of the amended claim recitation because the amendment is merely grammatical.

Objection to Drawings

Figures 6 and 7 were objected to, but replacement Figures 6 and 7 had been filed on June 4, 2003. Withdrawal of the objection is requested.

Claim Rejection -- 35 U.S.C. 112, First Paragraph

Claims 1, 3, 4, 6 and 10-12 were rejected as not enabled for the full scope of the claims because the Examiner asserted that the claims cover the use of TGFβ1, a TGFβ1 derivative or functionally equivalent substance. Applicants respectfully traverse the rejection partly because the claims no longer specifically recite the use of TGFβ1 derivatives or functionally equivalent substances.

The Examiner also asserted that, with TGFβ1 being a polypeptide, the method is enabled only when TGFβ1 is administered directly to the collateral arteries (not enabled for any route of administration). Applicants respectfully disagree. Applicants submit that an intravenous, intraperitoneal, subcutaneous, intramuscular, topical or intradermal administration of TGFβ1 will deliver TGFβ1 to contact the target organ or tissue because as long as the administered TGFβ1 is absorbed by the body, which there is no evidence or reason why it would not, there will be TGFβ1 contacting the target organ or

tissue to enhance arteriogenesis and/or the growth of collateral arteries and/or other arteries from preexisting arteriolar connections.

Regarding the method for enhancing the growth of arteries from preexisting arteriolar connections, the growth of arteries can take place in any preexisting arteriolar connection, not necessarily in merely the collateral arteries. The administration of TGFβ1 by any of the routes recited in claim 1 (even not directly to the collateral arteries) should be effective in contacting the target organ or tissue with TGFβ1. For instance, after an intraperitoneal, subcutaneous or intramuscular administration, some of the TGFβ1 (a peptide of 25 kD) molecules will be absorbed into the circulation and be transported to the target organ or tissue. Of course, intravenous administration will no doubt be effective in contacting the target organ or tissue with TGFβ1.

Withdrawal of the rejections under 35 U.S.C. 112, first paragraph, is requested.

Claim Rejection -- 35 U.S.C. 102(b)

Claims 1, 3 and 10-12 were rejected as anticipated by Roberts et al (PNAS 1986; 83:4167-4171) because Roberts et al. disclosed that subcutaneous administration of TGF-beta in newborn mice induced angiogenesis and activated fibroblasts causing formation of a granulation tissue (see Abstract). Applicants respectfully disagree that these claims lack novelty over Roberts et al.

Roberts et al. disclosed that TGF-beta administration formed a firm nodular tissue at the injection site and produced striking angiogenesis as shown by pronounced neovascularization with newly formed capillary loops (see right column, page 4168, lines 5-21; the legend of Fig. 1C, page 4169). Roberts et al. stated that the angiogenic

and fibrotic responses were consistent with characteristic proliferation of fibroblasts and small blood vessels that occur during wound healing and tissue repair (see right column, page 4168, lines 18-21). Roberts et al. did not teach that TGF-beta was effective in inducing the formation of arteries because Roberts et al. concentrated on capillary loops, but **"arteries" are not capillary loops or small blood vessels**. A person skilled in the art would understand that the term "angiogenesis" as used by Roberts et al. does not include the growth of new arteries (the data presented by Roberts et al. did not support any notion that TGF-beta enhances the growth of arteries). Since both the "arteriogenesis" and the growth of arteries enhanced by the method of claim 1 involve the formation of arteries, Roberts et al. failed to anticipate claims 1, 3 and 10-12.

The Examiner did not give any patentable weight to "wherein said method is applied to a subject suffering from a vascular disease or a cardiac infarct or a stroke" (in claims 10 and 11) and "wherein said method is applied to a subject during or after exposure to an agent or radiation or surgical treatment which damage or destroy arteries" (in claim 12). Applicants respectfully traverse the rejection of claims 10-12 because "wherein said method is applied to a subject suffering from a vascular disease or a cardiac infarct or a stroke" or "wherein said method is applied to a subject during or after exposure to an agent or radiation or surgical treatment which damage or destroy arteries" is a claim limitation in the body of the claim, where the claim limitation defines a step of the claimed method. For instance, in the method of claims 10-12, the TGFβ1 is applied to "a subject suffering from a vascular disease or a cardiac infarct or a stroke" in claims 10 and 11, or applied to "a subject during or after exposure to an agent or

radiation or surgical treatment which damage or destroy arteries" in claim 12. These are positive recitations that describe some of the elements of the claimed invention, and should be given patentable weight as a result. Since the newborn mice treated with TGF-beta in the studies of Roberts et al. were not "a subject suffering from a vascular disease or a cardiac infarct or a stroke" or "a subject during or after exposure to an agent or radiation or surgical treatment which damage or destroy arteries", this is an additional reason why Roberts et al. failed to anticipate claims 10-12.

Withdrawal of the anticipatory rejections is requested.

Claim Rejection -- 35 U.S.C. 103

Claims 1, 4 and 6 were rejected as obvious over Roberts et al. in further view of Asahara (an abstract of Circulation, 1995; 92 (9, Suppl.):II365). Applicants respectfully traverse the rejection.

For the obviousness rejection of claim 1, the Examiner relied on the reasons set forth in the above anticipatory rejections without any further explanation for the obviousness. The obviousness rejection of claim 1 should be withdrawn because, based on the teaching of Roberts et al. that TGF-beta was effective in inducing the formation of small blood vessels and capillary loops, it would not have been reasonably expected that TGFβ1 is effective in inducing the formation of arteries which are larger than the new blood vessels shown in the study of Roberts et al. A person of ordinary skill in the art would have no motivation, based on Roberts et al., to contact an organ or tissue with TGFβ1 to enhance arteriogenesis or arterial growth from preexisting collateral arteriolar connections in order to arrive at the method of claim 1.

For the obviousness rejection of claims 4 and 6, the Examiner acknowledged that Roberts et al. did not teach the co-administration of TGF-beta and another growth factor. The Examiner relied on Asahara which disclosed that two angiogenic mitogens, vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), given almost at the same time in the internal iliac artery in an ischemic hind limb of a rabbit having had surgical induction of unilateral hind limb ischemia, acted synergistically in increasing the luminal diameter of a stem collateral artery in the thigh of the ischemic hind limb (lines 10-20 from the bottom of the Abstract). The Examiner asserted that a person of ordinary skill would have modified the method of Roberts et al. by co-administration of TGF-beta and VEGF or bFGF with a reasonable expectation of success rendering claims 4 and 6 obvious. The Examiner stated that the motivation to modify the method of Roberts et al. was provided by Asahara which indicated that combinations of angiogenic mitogens may have important implications for the treatment of severe arterial insufficiency not amenable to direct revascularization. Applicants respectfully disagree.

Regarding claims 4 and 6, there would have been no motivation to modify the method of Roberts et al. because the method of Roberts et al. was **aimed merely at validating a hypothesis** that TGF-beta is an important mediator of tissue repair (see the last sentence of the Abstract of Roberts et al.). Roberts et al. did not concern with the treatment of severe arterial insufficiency. A person of ordinary skill in the art would have no desirable reason of adding VEGF or bFGF to the method of Roberts et al. because the person would have known that the VEGF or bFGF would very likely complicate the picture so that the person would not know whether a certain biological

effect was caused by TGF-beta or the other growth factor added. The person also would not have been motivated to administer VEGF or bFGF along with TFG-beta in the method of Roberts et al. because adding VEGF or bFGF would not help to validate the hypothesis that TGF-beta is an important mediator of tissue repair.

Withdrawal of the obviousness rejections is requested.

Conclusion

In view of the amendment and the above reasoning, applicants submit that the application is in a condition for allowance. A Notice of Allowance is believed in order.

In the event that the filing of this paper is not deemed timely, applicants petition for an appropriate extension of time. Any petition fee for the extension of time and any other fees that may be required in relation to this paper can be charged to Deposit Account No. 01-2300, referencing Docket No. 025896-00002.

Respectfully submitted,

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